

E2F1 Inhibitor to Prevent Apoptosis

Abstract

Provided is a method and vector for modulating apoptosis in a target cell population. Flavopiridol treatment leads to apoptosis via a mechanism associated with downregulation of Mcl-1. E2F1 leads to transcriptional repression of Mcl-1 and subsequently apoptosis. Given the ability of cyclin/cyclin-dependent kinase 2 antagonists to kill transformed cells, flavopiridol may stabilize E2F1 and enhance apoptosis via repression of Mcl-1. Flavopiridol is associated with a dose-dependent increase in E2F1 protein levels, a corresponding reduction in Mcl-1, and apoptosis in lung carcinoma cells. Treatment of cells with 200 nM flavopiridol results in the rapid elevation of E2F1 and reduction in Mcl-1 levels within 12 hours of treatment. The elevation of E2F1 and reduction in Mcl-1 clearly precedes the induction of apoptosis. Cell lines that constitutively express Mcl-1 under the control of the cytomegalovirus promoter have no reductions in Mcl-1 levels with flavopiridol treatment and are resistant to apoptosis induced by flavopiridol .